## REMARKS

Claims 1-62 are pending in the application. Claims 1,2, 12-16, 33, 34 and 43-47 are drawn to an elected invention. Among these, only claims 1 and 33 are independent claims.

Applicants have narrowed claims 1 and 33 so that the definitions of $R_{17}$ and $R_{17'}$ do not include "oxo," and the definition of $R_3$ does not include "-CO-O-" as a variable for "Y." Support for these amendments can be found throughout the Specification, e.g., page 6, lines 7-22, and in the original claims as filed, e.g., claims 14-16 and claims 45-47. Applicants have also amended claims 1 and 33 to clarify the definitions of $R_4$ and $R_{4'}$ with respect to the "oxo" substituent (see discussion under 35 U.S.C. 112, second paragraph). These amendments introduce no new matter.

Reconsideration of the application in view of the above amendments and the following remarks is respectfully requested.

Rejections under 35 U.S.C. 112, second paragraph

Claims 1, 2, 12-14, 33, 34, and 43-45 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite. Specifically, the Examiner stated that "the instant claims are confusing because they recite $R_4$, $R_{4'}$, $R_{17}$ and $R_{17'}$ independently oxo...if $R_4$ and $R_{4'}$ are independently oxo, the valence of the carbon atom to which they are attached would [be] incorrect" (Office Action, page 2. lines 14-16). Applicants have amended the definitions of $R_4$ and $R_{4'}$ to read "...$R_4$ together with $R_{4'}$ is oxo" and "...$R_{4'}$ together with $R_4$ is oxo" respectively to clarify that $R_4$ and $R_{4'}$, which occupy the same carbon atom, are not independently oxo, i.e., C=O, but when taken together can form an oxo group. The definitions of $R_{17}$ and $R_{17'}$ have been amended so as not to include "oxo."

Rejections under 35 U.S.C. 102(b)

The Examiner has rejected claims 1, 2, 12-14, 33, 34, and 43-45 under 35 U.S.C. 102(b) as being anticipated by Daynes et al. US 5,562,910 (Daynes). The Examiner has also rejected

claims 1, 12, 33 and 43 under 102(b) as being anticipated by Wildi US 2,698,853 (Wildi) and Miller et al. US 6,369,247 B1 (Miller).

Daynes discloses 7-keto-dehydroepiandrosterone-3 sulfate. Applicants have amended claims 1 and 33 so that the definitions of $R_{17}$ and $R_{17'}$ do not include "oxo," i.e., C=O. As a result, steroids possessing the dehydroepiandrosterone skeleton (C-17 oxo ), i.e., 7-keto-dehydroepiandrosterone-3 sulfate, do not fall within the scope of the amended claims. This amendment is supported by, e.g., the Specification, page 6, lines 7-22, since Applicants' disclosed species, 7-keto-cholesterol-3-sulfate, contains the cholesterol skeleton (no C-17 oxo) and not the dehydroepiandrosterone skeleton. Therefore, Daynes does not anticipate independent claims 1 and 33. Since claims 2, 12-14 depend from claim 1 and claims 34, 43-45 depend from claim 33, these claims also are not anticipated by Daynes.

Wildi and Miller disclose 7-cholestenone acetate. Applicants have amended claims 1 and 33 so that the definition of $R_3$ does not include "-CO-O-" as a variable for "Y." As a result, 7-cholestenones possessing a carboxylic acid-esterified hydroxyl group at C-3, i.e., 7-cholestenone acetate, do not fall within the scope of the amended claims. This amendment is again supported by, e.g., the Specification, page 6, lines 7-22, since Applicants' disclosed species, 7-keto-cholesterol-3-sulfate, contains a sulfate group at C-3 and not a carboxylic acid-esterified hydroxyl group at C-3. Therefore, Wildi and Miller do not anticipate independent claims 1 and 33. Since claim 12 depends from claim 1 and claim 43 depends from claim 33, these claims also are not anticipated by Wildi and Miller.

Rejections under 35 U.S.C. 103(a)

The Examiner has rejected claims 1,2, 12-16, 33, 34, and 43-47 under 35 U.S.C. 103(a) as being unpatentable over Miller. According to the Examiner:

> "The instant claims differ from the reference by reciting compounds not exemplified by the reference. However, the reference teaches the 3-position can be any esterified hydroxy group (see especially col. 5, lines 9-25). The ordinary artisan in the art at the time of the invention would readily envisage the utilization of a wide variety of esters, including those of the instant claims, with the reasonable expectation of obtaining that the desired 5-ene-7-keto as taught by Miller. In addition, an ester is ordinarily unpatentable over the alcohol from

> which it is derived because esterification is widely practiced in the chemical art. Ex parte Korten, 71 USPQ 173." (Office Action, page 4 lines 15-24 – page 5, lines 1-2)

Miller discloses a process for the allylic oxidation of steroidal compounds. Specifically, the oxidation of the alkenyl steroids of Formula (I) to the enones of Formula (II) is described (see Exhibit A). Only two species of Formula (II) are specifically described in Miller, both of which contain an acetate group (i.e., $CH_3C(O)O$-) as substituent "Y" (i.e. the C-3 position, see Exhibit A). Miller also explicitly points out that the Formula (II) compounds are synthetic intermediates useful for making downstream steroidal 5α-reductase inhibitors:

> "The oxidation of Δ-5-steroidal alkenes to the corresponding enones is an important step in the synthesis of steroid end products useful as 5α-reductase inhibitors" (emphasis added, column 1, lines 47-49).

> "Compounds of Formula (II) are useful as intermediates in the preparation of 7β-substituted 3-keto-4-azasteroid compounds, such as those which are 5α-reductase inhibitors. 5α-reductase inhibitors are useful in the treatment of hyperandrogenic disorders..." (emphasis added, column 2, lines 23-26; this statement is repeated almost verbatim at column 5, lines 25-27).

Miller also presents an eight-step synthesis of 4,7β-dimethyl-4-aza-α-cholestanone in which the allylic oxidation step (Figure 4) is the first step of the synthetic sequence.

Applicants respectfully traverse and point out the decision in *In re Lalu*, summarized in the passage below:

> "...if the prior art merely discloses compounds as intermediates in the production of a final product, one of ordinary skill in the art would not have been motivated to stop the reference synthesis and investigate the intermediate compound with an expectation of arriving at claimed compounds which have different uses" (MPEP 2144.09; *In re Lalu*, 747 F.2d 703, 223 USPQ 1257 (Fed. Cir. 1984)).

In other words, structurally similar compounds would not have been *prima facie* obvious over prior art compounds that have utility only as intermediates. Clearly, the only utility disclosed for

the two 5-ene-7-ones disclosed in Miller is their usefulness as synthetic intermediates for the production of 5 α-reductase inhibitors. Therefore, the claimed compounds, which are unexpectedly useful for treating hypocholesterolemia, are not rendered obvious by the Miller compounds, which are useful only as early synthetic intermediates in the synthesis of 5α-reductase inhibitors. In other words, claim 1 would not have been obvious over Miller. Since claims 2 and 12-16 depend from claim 1, they are also not rendered obvious by Miller.

Claim 33 is directed to a pharmaceutical composition comprising the compounds of claim 1 and a pharmaceutically acceptable carrier. There is no disclosure in Miller that would suggest to one of ordinary skill in the art that the intermediary Formula (II) compounds, or pharmaceutical compositions containing these compounds, would be useful for or should be tested for treating hyperandrogenic disorders, the disclosed utility of the 5 α-reductase inhibitors. Further, there is certainly no suggestion in Miller that the Formula (II) compounds, or pharmaceutical compositions containing these compounds, would be useful for or should be tested for treating hypocholesterolemia, which again is the unexpected utility of the compounds of claim 1. Therefore, claim 33 is not rendered obvious by Miller. Since claims 34, 43-47 depend from claim 33, they are also not rendered obvious by Miller.

## CONCLUSION

Applicants submit that all of the pending claims under consideration are in condition for allowance for the reasons set forth above.

Attached hereto is a marked-up version of the changes being made by the current amendments.

Pursuant to 37 CFR §1.136, applicant hereby petitions that the period for response to the action dated August 23, 2002, be extended for two months to and including January 23, 2003.

Enclosed is a $205 check for the Two-Month Petition for Extension of Time fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 1-23-02

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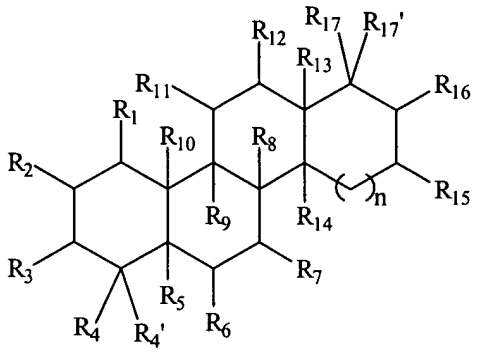
## Version with markings to show changes made

In the claims:

Claims 1 and 33 has been amended as follows:

1. A compound of formula (1):




(1)

wherein

each of $R_1$, $R_2$, [$R_4$, $R_{4'}$,] $R_7$, $R_{11}$, $R_{12}$, $R_{15}$, and $R_{16}$, [$R_{17}$, and $R_{17'}$,] independently, is hydrogen, hydroxy, amino, carboxyl, oxo, halo, sulfonic acid, -O-sulfonic acid, or alkyl that is optionally inserted with -NH-, -N(alkyl)-, -O-, -S-, -SO-, -$SO_2$-, -O-$SO_2$-, -$SO_2$-O-, -$SO_3$-O-, -CO-, -CO-O-, -O-CO-, -CO-NH-, -CO-N(alkyl)-, -NH-CO-, or -N(alkyl)-CO-, and further optionally substituted with hydroxy, halo, amino, carboxyl, sulfonic acid, or -O-sulfonic acid;

$R_4$ is hydrogen, hydroxy, amino, carboxyl, halo, sulfonic acid, -O-sulfonic acid, alkyl that is optionally inserted with -NH-, -N(alkyl)-, -O-, -S-, -SO-, -$SO_2$-, -O-$SO_2$-, -$SO_2$-O-, -$SO_3$-O-, -CO-, -CO-O-, -O-CO-, -CO-NH-, -CO-N(alkyl)-, -NH-CO-, or -N(alkyl)-CO-, and further optionally substituted with hydroxy, halo, amino, carboxyl, sulfonic acid, or -O-sulfonic acid; or $R_4$ together with $R_{4'}$ is oxo;

$R_{4'}$ is hydrogen, hydroxy, amino, carboxyl, halo, sulfonic acid, -O-sulfonic acid, alkyl that is optionally inserted with -NH-, -N(alkyl)-, -O-, -S-, -SO-, -$SO_2$-, -O-$SO_2$-, -$SO_2$-O-, -$SO_3$-O-, -CO-, -CO-O-, -O-CO-, -CO-NH-, -CO-N(alkyl)-, -NH-CO-, or -N(alkyl)-CO-, and further optionally substituted with hydroxy, halo, amino, carboxyl, sulfonic acid, or -O-sulfonic acid; or $R_{4'}$ together with $R_4$ is oxo;

each of $R_{17}$, and $R_{17'}$, independently, is hydrogen, hydroxy, amino, carboxyl, halo, sulfonic acid, -O-sulfonic acid, or alkyl that is optionally inserted with -NH-, -N(alkyl)-, -O-, -S-, -SO-, -$SO_2$-, -O-$SO_2$-, -$SO_2$-O-, -$SO_3$-O-, -CO-, -CO-O-, -O-CO-, -CO-NH-, -CO-N(alkyl)-, -NH-CO-, or -N(alkyl)-CO-, and further optionally substituted with hydroxy, halo, amino, carboxyl, sulfonic acid, or -O-sulfonic acid;

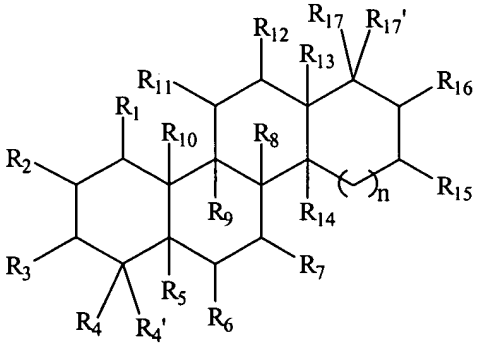
$R_3$ is X-Y-, wherein X is hydrogen, amino, carboxyl, halo, sulfonic acid, -O-sulfonic acid, or alkyl; Y is -S-, -NH-, -N(alkyl)-, -SO-, -$SO_2$-, -O-$SO_2$-, -$SO_2$-O-, -$SO_3$-O-, -CO-, [-CO-O-], -O-CO-, -CO-NH-, -CO-N(alkyl)-, -NH-CO-, or -N(alkyl)-CO-;

$R_5$ and $R_6$, together, are -O-; or $R_5$ and $R_6$, together, are a double bond between C-5 and C-6, and $R_7$ is oxo;

each of $R_8$, $R_9$, $R_{10}$, $R_{13}$, and $R_{14}$, independently, is hydrogen, alkyl, haloalkyl, hydroxyalkyl, alkoxy, hydroxy, or amino; and

n is 0, 1, or 2.

33. A pharmaceutical composition comprising a compound of formula (1):




(1)

wherein:

each of $R_1$, $R_2$, [$R_4$, $R_{4'}$,] $R_7$, $R_{11}$, $R_{12}$, $R_{15}$, and $R_{16}$, [$R_{17}$, and $R_{17'}$,] independently, is hydrogen, hydroxy, amino, carboxyl, oxo, halo, sulfonic acid, -O-sulfonic acid, or alkyl that is optionally inserted with -O-, -S-, -NH-, -N(alkyl)-, -SO-, -$SO_2$-, -O-$SO_2$-, -$SO_2$-O-, -$SO_3$-O-, -CO-, -CO-O-, -O-CO-, -CO-NH-, -CO-N(alkyl)-, -NH-CO-, or -N(alkyl)-CO-, and further optionally substituted with hydroxy, halo, amino, carboxyl, sulfonic acid, or -O-sulfonic

$R_4$ is hydrogen, hydroxy, amino, carboxyl, halo, sulfonic acid, -O-sulfonic acid, alkyl that is optionally inserted with -NH-, -N(alkyl)-, -O-, -S-, -SO-, $-SO_2-$, $-O-SO_2-$, $-SO_2-O-$, $-SO_3-O-$, -CO-, -CO-O-, -O-CO-, -CO-NH-, -CO-N(alkyl)-, -NH-CO-, or -N(alkyl)-CO- , and further optionally substituted with hydroxy, halo, amino, carboxyl, sulfonic acid, or -O-sulfonic acid; or $R_4$ together with $R_{4'}$ is oxo;

$R_{4'}$ is hydrogen, hydroxy, amino, carboxyl, halo, sulfonic acid, -O-sulfonic acid, alkyl that is optionally inserted with -NH-, -N(alkyl)-, -O-, -S-, -SO-, $-SO_2-$, $-O-SO_2-$, $-SO_2-O-$, $-SO_3-O-$, -CO-, -CO-O-, -O-CO-, -CO-NH-, -CO-N(alkyl)-, -NH-CO-, or -N(alkyl)-CO-, and further optionally substituted with hydroxy, halo, amino, carboxyl, sulfonic acid, or -O-sulfonic acid; or $R_{4'}$ together with $R_4$ is oxo;

each of $R_{17}$, and $R_{17'}$, independently, is hydrogen, hydroxy, amino, carboxyl, halo, sulfonic acid, -O-sulfonic acid, or alkyl that is optionally inserted with -NH-, -N(alkyl)-, -O-, -S-, -SO-, $-SO_2-$, $-O-SO_2-$, $-SO_2-O-$, $-SO_3-O-$, -CO-, -CO-O-, -O-CO-, -CO-NH-, -CO-N(alkyl)-, -NH-CO-, or -N(alkyl)-CO-, and further optionally substituted with hydroxy, halo, amino, carboxyl, sulfonic acid, or -O-sulfonic acid;

$R_3$ is X-Y-, wherein X is hydrogen, amino, carboxyl, halo, sulfonic acid, -O-sulfonic acid, or alkyl; Y is -S-, -NH-, -N(alkyl)-, -SO-, $-SO_2-$, $-O-SO_2-$, $-SO_2-O-$, $-SO_3-O-$, -CO-, [-CO-O-, ] -O-CO-, -CO-NH-, -CO-N(alkyl)-, -NH-CO-, or -N(alkyl)-CO-;

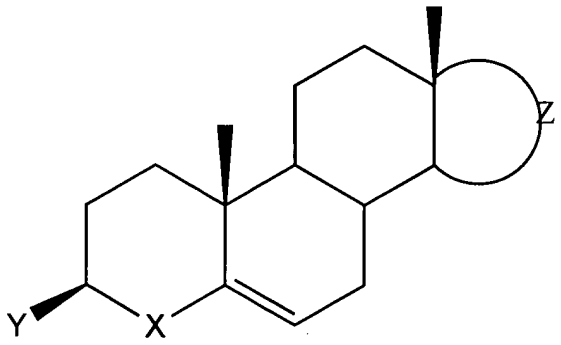
$R_5$ and $R_6$, together, are -O-; or $R_5$ and $R_6$, together, are a double bond between C-5 and C-6, and $R_7$ is oxo;

each of $R_8$, $R_9$, $R_{10}$, $R_{13}$, and $R_{14}$, independently, is hydrogen, alkyl, haloalkyl, hydroxyalkyl, alkoxy, hydroxy, or amino; and

n is 0, 1, or 2;

and a pharmaceutically acceptable carrier.

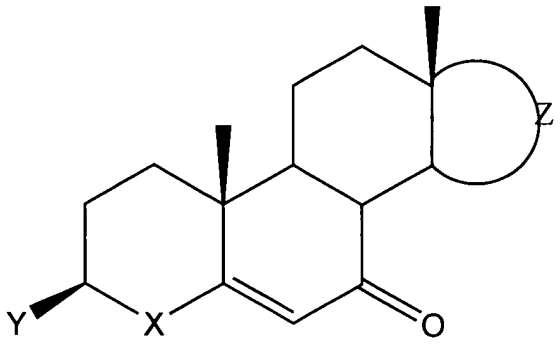
EXHIBIT A




1) Ru catalyst

2) t-BuOOH

(I)




(II)